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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,944	03/25/2004	Luc J. Farmer	VPI/02-133 US	6398

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/809,944	FARMER ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17-30,34 and 36-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17-30,34 and 36-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050902*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-15, 17-30, 34 and 36-44 are pending in this application.

Election/Restrictions

Applicant's election **without** traverse of Group I (claims drawn to monocyclic pyrimdine compounds of formula I wherein R^1 and R^2 are independent substituents and are NOT taken together to form a ring) in the reply filed on May 30, 2006 is acknowledged.

Note: It is noted that applicant amended claim 1 to remove non-elected subject matter from the definitions of R^1 and R^2. The claim generically contains non-elected subject matter, see the definition of R^1 and R^2, each of which is defined to be " TR " and in the definition of R it is recited that 'two occurrences of R taken together form an optionally substituted saturated, partially unsaturated or fully unsaturated 3-8 membered ring having 0-3 heteroatoms' and therefore, the claims contain non-elected subject matter, which must be deleted to avoid generic overlap.

Applicant's election of the species **I-4** is acknowledged. As the elected species was not found in the prior art, the search was expanded to the genus of the elected invention of Group I.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a compound of formula (I) and a method of treating rheumatoid arthritis or asthma comprising the step of administering a compound of formula (I), does not reasonably provide enablement for a composition comprising a compound in an amount to detectably inhibit SYK or ZAP-70 protein kinase activity; a composition comprising an additional therapeutic agent as recited in claim 38; a method of inhibiting SYK or ZAP-70 kinase activity in a biological sample generally; or a method of treating or lessening the severity of all types of diseases of claims 41-43. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant composition claim 38 recites a particular intended use for the composition, i.e., 'detectably inhibit SYK or ZAP-70 protein kinase activity', which according to the specification is directed to a wide list of therapeutic methods and the specification, does not provide enablement for all the listed disorders. When a compound or composition claim is

limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

The instant claim 39 is drawn to 'a composition comprising a compound of formula I and additionally a second therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, ...' and the specification pages 51-52 provide some examples of the additional therapeutic agent intended by the claim, however, the scope of the claim includes therapeutic agents that are known and those that may be discovered in future, for which there is no enablement. Further, the entire scope of the therapeutic activity intended for the compounds of the invention is not enabled for the reasons provided below.

The instant claim 40 is drawn to 'a method of inhibiting SYK or ZAP-70 kinase activity in a biological sample by contacting the biological sample with a compound of formula (I) or a composition comprising the compound of formula (I)'. The examples in pages 55-56 in the specification provide *in vitro* assays to measure the SYK and ZAP-70 kinase inhibition activity of some of the exemplified compounds of the instant invention. The term "biological sample" is defined in the specification (page 52, paragraph [00135]) to 'include, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof'. As can be seen from the definition of the term, without limitation it reads on many types of biological samples, including mammals or animals and therefore, they are seen to encompass methods wherein the compound is administered to an animal. The instant claim appears to be a 'reach through' claim.

Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The testing assays provided in the specification on pages 55-56 are related to SYK and ZAP-70 kinase inhibition in a standard coupled enzyme assay, however, there is no data of the tested compounds. Applicant did not state on record or provide any guidance that the assay provided is correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification page 46, the activity data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of the kinases.

The instant claims 41-43 are drawn to "a method treating or lessening the severity of lepromatous leprosy, atopical dermatitis, ... Crohn's disease, ulcerative colitis, ... multiple sclerosis, ... leukemia, lymphoma, ... atherosclerosis ....". The use disclosed in the specification is as SYK and ZAP-70 kinase inhibitors, useful to treat a large list of diverse diseases. Test assays and procedures are provided in the specification in pages 55-56 related to SYK and ZAP-70 kinase inhibition and it was concluded that the compounds of the invention exhibit inhibitory activity, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. The diseases and disorders encompassed by the instant claims include various types of ulcerative colitis, multiple sclerosis, atherosclerosis, leukemia, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of

compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how all these assorted types diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the large list of diseases embraced by the claims having diverse mechanisms.

For example, the instant claims are drawn to 'treating leukemia, lymphoma, etc.' which includes treatment of all types of cancers of blood, lymphocytes, etc. A 'cancer' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004).

Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that "pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles" see page 585, col. 2, lines 33-36.

Further, the list of the diseases includes multiple sclerosis, which has traditionally been very difficult or impossible to treat effectively with chemotherapeutic agents. See e.g., Casanova et al. (PubMed Abstract enclosed) state that "Multiple Sclerosis (MS) is a disorder in which the pathogenesis is not clearly understood", see the abstract. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating or lessening the severity' effect of a 'disease' solely based on the inhibitory activity disclosed for the compounds.

Atherosclerosis is a common form of arteriosclerosis associated with the formation of atheromas which are deposits of yellow plaques containing cholesterol, lipids, and lipophages within the intima and inner media of arteries. This results in a narrowing of the arteries, which

reduces the blood and oxygen flow to the heart and brain as well as to other parts of the body and can lead to a heart attack, stroke, or loss of function or gangrene of other tissues. The claims are also directed to 'a method of treating or lessening severity of type I diabetes' and the specification did not provide any competent tests or data to establish that the compounds have the claimed activity.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment or prevention. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in a recent article (Exp. Opin. Ther. Patents, 1997) stated that "The concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation.", see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-30, 34 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 17, there is no definition provided for the variable " n ". The discrepancy is also present in claim 23. Further, claim 17 does not end with a period.
2. Claim 34 recites the limitation "c) R^4 is $(CH_2)_n$halogen, ..."" in page 17, lines 1-7. There is insufficient antecedent basis for this limitation in claim 1 on which claim 34 is dependent (via claims 17 and 23). As per claim 1, "R^4 is hydrogen".

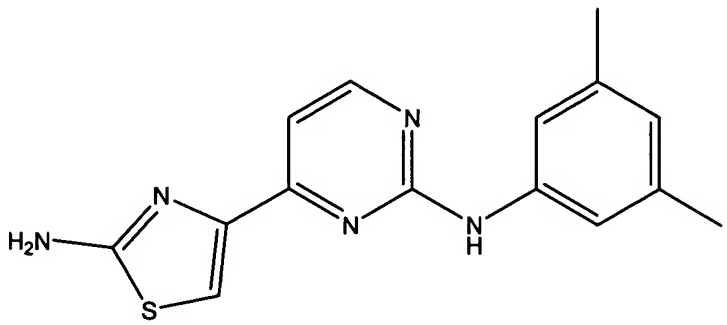
3. In claim 36, some of the structural formulae are incomplete and/or illegible, see the formulae for compounds I-53 (page 22), I-65 (page 24), etc.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-15, 17-30, 34 and 37-44 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Fraley et al., WO 03/011838. The instant claims read on reference disclosed compounds, see the compound disclosed in the last line of page 11 (structural formula depicted below for convenience):



4-(2-amino-1,3-thiazol-4-yl)-N-(3,5-dimethylphenyl)pyrimidin-2-amine

2. Claims 1, 4, 7-8, 10-12 and 37-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Cao et al., WO 04/041813 (claiming benefit of U.S. Provisional application filing date of October 30, 2002). The instant claims read on reference disclosed compound, see the compound I-B-265 in page 73.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15 and 37-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al., WO 97/19065. The reference teaches substituted 2-anilinopyrimidine compounds that are structurally analogous to instantly claimed compounds. See the compounds of formula (1) and the corresponding Examples 8, 26, etc. The compounds are taught to be useful as pharmaceutical therapeutic agents for the treatment of rheumatoid arthritis, asthma etc., see page 14, lines 30+. The instant compounds differ from the reference compounds by having a 4-thiazolyl substituent attached to the pyrimidinyl core as compared to the 2-thiazolyl or 5-thiazolyl groups in the reference. In other words, the instantly claimed compounds have a different point of attachment on the thiazolyl group as compared to the reference compounds, and therefore, the instantly claimed compounds are positional isomers of the reference compounds. It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are positional isomers of the

reference compounds. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds, i.e., as pharmaceutical agents. It has been held that a compound, which is structurally isomeric with a compound of prior art is prima facie obvious absent unexpected results. *In re Finley*, 81 USPQ 383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950); *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15, 17-30, 34 and 36-44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-47 of

copending Application No. 10/809,946. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to structurally analogous compounds. The reference claims are drawn to substituted 2-anilinopyrimidine compounds that are structurally analogous to instantly claimed compounds. See the compounds of formula (I). The compounds are taught to be useful as pharmaceutical therapeutic agents for the treatment of rheumatoid arthritis, asthma etc., see claims 44-47. The instant compounds differ from the reference compounds by having a 4-thiazolyl substituent attached to the pyrimidinyl core as compared to the 2-thiazolyl group in the reference application. In other words, the instantly claimed compounds have a different point of attachment on the thiazolyl group as compared to the reference compounds, and therefore, the instantly claimed compounds are positional isomers of the reference compounds. It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are positional isomers of the reference compounds. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds, i.e., as pharmaceutical agents.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Receipt is acknowledged of the Information Disclosure Statement filed on September 2, 2005 and a copy is enclosed herewith.

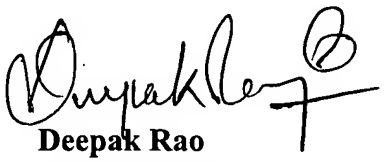
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deepak Rao
Primary Examiner
Art Unit 1624

August 3, 2006